IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Nadeson et al.	Confirmation No.:	9722
Serial No.:	10/574,438	Group Art Unit:	1614
Filing Date:	06/25/2007	Examiner:	Jagoe, Donna A

Title: METHODS AND COMPOSITIONS

DECLARATION OF MICHAEL STEPHEN ROBERTS UNDER 37 C.F.R. § 1.132

I, Michael Stephen Roberts, hereby declare as follows:

1. I am a Professor in the School of Medicine, and an Australian National Health & Medical Research Council (NHMRC) Senior Principal Research Fellow and Director of the Therapeutics Research Unit at the University of Queensland, St Lucia, Queensland, Australia. I am also an Adjunct Professor at the University of Canberra, Canberra, Australian Capital Territory, Australia and am a Visiting Professor of the University of Lyon, France. I hold a Bachelor of Pharmacy, Master of Science, Doctor of Philosophy, Doctor of Science, Diploma of Tertiary Education and a Master of Business Administration. I have particular expertise in pharmacology and toxicology. My Curriculum Vitae is attached as **Exhibit A** which evidences my area of academic credentials.

2. I have specialist expertise in the design of topical products for therapeutic uses.

3. I have been briefed by patent counsel in respect of US Patent Application No. 10/574,438 assigned to CNSBio Pty Ltd and the Official Action which has issued from the US Patent and Trademark Office on 29 September, 2009. I am aware that US Patent Application No. 10/574,438 teaches the treatment of neuropathic pain by the administration of flupirtine in a dosage range of 200mg to 600mg per day. In the Official Action, the Examiner has raised a novelty rejection against Claims 43 to 45 and 48 and an allegation that Claims 46 and 47 are obvious in light of US Patent No. 6,916,482 (Klose *et al.*).

4. In particular, the Examiner has alleged that (*sic*) "Klose *et al.* teach an analgesic composition for the treatment of neuropathic pain comprising flupirtine and other

opioid analgesics". US Patent No. 6,916,482 relates to a transdermeral drug delivery system for an analgesic.

5. For the reasons outlined below, despite the fact that flupirtine meets the desirable criteria for being able to be transdermally delivered (i.e. it is a small, lipophilic molecule), it would not be possible to deliver a daily dose of 200mg to 600mg by topical administration in accordance with the method disclosed by Klose *et al.* Data indicate that transdermal delivery of flupirtine would not be effective.

6. Flupirtine has a molecular weight (MW) of 304 and is moderately lipophilic, as defined by the logarithm of the octanol-water partition coefficient (log P) of 1.99. Such physical properties would normally be required for compounds to be delivered by transdermal administration. For instance, the range of MW for the transdermal solutes presently on the market, is 162 to 468 and the range for log P is 1.17 to 5.19.[1]. A consideration in delivering a drug transdermally is the percentage of the dose entering the skin that actually reaches the blood stream. It may be as low as 25% as found for selegiline . It should be noted that 90% of a given oral dose of flupirtine reaches the blood stream [2].

7. Flupirtine acts centrally in the brain in the treatment of neuropathic pain. In general, due to the significant barrier properties of the human stratum corneum, candidate molecules delivered by the skin are usually potent, small and lipid solutes. The current high oral doses of flupirtine being used in the management of neuropathic pain is direct evidence that flupirtine is not a potent drug. Examples of solutes currently delivered across the skin include: buprenorphine, clonidine, estradiol, fentanyl, isosorbide dinitrate, methyl phenidate, nicotine, nitroglyucerin, oxybutynin, rivastigmine, rotigotine, scopolamine, selegiline, testosterone, timolol and triprolidone. [2]

8. The importance of potency as a critical determinant of the viability of flupirtine being used a transdermal formulation is emphasized by the fact that an order of magnitude (<10X) higher plasma level of flupirtine required to produce a therapeutic effect compared to the best of the currently marketed drugs. The highest steady state plasma level of 0.1 mg/L reported for the current transdermal drugs on the market is for testosterone, a slightly smaller and more lipophilic than flupirtine [1]. In contrast, the predicted steady state plasma concentration for a minimum 300 mg daily dose for flupirtine is 1.86 mg/L, based on

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1 Roberts MS and Walters KA. *Dermal Absorption and Toxicity Assessment. 2nd ed* , Informa, NY, 2008, p11.
2 Abrams *et al.* Pharmacokinetics of flupirtine in elderly volunteers and in patients with moderate renal impairment. *Postgraduate Medical Journal* (1988), 64(751), 361-3.

its clearance of 1.6 mL/min/kg [3] in a 70kg person [4]. This calculation should occur for chronic dosing as no significant accumulation in plasma concentrations occurs on repeated oral dosing [5]. Plasma levels are proportional to flupirtine doses, assessed using doses of 50, 100, 200, and 300 mg [6]. The estimated steady state level for flupirtine after 300mg/day is similar to the observed peak plasma concentration after a single oral dose of 200mg in volunteers [5] and in patients [7], as may be anticipated from flupirtine having a half life of about 8.5 hr [6].

9. It should be emphasized that after 12 months on a mean daily dose of 300mg/day, complete pain relief was only found in 18 to 25% of patients, indicating that for better pain relief, a higher dose is likely to be required [8]. Further, as a consequence, the potency differential between transdermal marketed products and flupirtine is even more marked than estimated above.

10. Data disclosed in US Patent No. 6,916,486 for fentanyl show that this transdermal delivery system would not provide an adequate level of flupirtine in the blood stream for a chronic clinical response, assuming a minimum dose requirement of 300mg/day and a neuropathic effect. This patent revealed that 7.5% fentanyl (MW 336) and log P value of 3.93 had a steady state skin flux of about 2$\mu g/cm^2/hr$. If this was applied over the maximum specified area defined in the patent of 800 cm^2, the amount delivered per day could be 38.4 mg (i.e. 2 X 800 X 24 hr). The actual delivery rate from the largest commercial patches (40cm^2) of fentanyl is ~ 2.4 mg/day [9], i.e. the patch rate of ~2.5 $\mu g/cm^2/hr$ is almost identical to that for the patent. If fentanyl was used as a surrogate for flupirtine absorption, recognizing that its size (MW 304) and lipophilicity (log P 1.99) is similar, the best scenario which could be achieved of 1/10 the dose required, or in the more usual case of a maximum patch size of 40 cm^2, a delivery rate 1/100th that required. Other transdermal drugs also have a maximum of about 40cm^2, as illustrated by Estraderm (44cm^2) [10] and Nitro-Dur (40cm^2) [11].

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3 Obach *et al.* Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. *Drug Metabolism and Disposition* (2008), 36(7), 1385-1405.
4 Steady state plasma concentration=dosing rate/clearance.
5 Hlavica, P.; Niebch, G. Studies on the pharmacokinetics and biotransformation of the analgesic flupirtine in man. *Arzneimittel-Forschung* (1985), 35(1), 67-74.
6 Niebch *et al.* Dose-proportional plasma levels of the analgesic flupirtine maleate in man: application of a new HPLC assay. *Arzneimittel-Forschung* (1992), 42(11), 1343-5.
7 Abrams *et al.* Pharmacokinetics of flupirtine in elderly volunteers and in patients with moderate renal impairment. *Postgraduate Medical Journal* (1988), 64(751), 361-3.
8 Friedel, Heather A.; Fitton, Andrew. Flupirtine: a review of its pharmacological properties, and therapeutic efficacy in pain states. *Drugs* (1993), 45(4), 548-69.
9 http://www.medsafe.govt.nz/Profs/Datasheet/d/durogesictts.htm.
10 http://www.appco.com.au/guide/Book%20Spread.pdf.
11 http://www.sch-plough.com/documents/18143666_Nitro-Dur_PI.pdf.

It is suggested that spraying 800cm^2 or 0.86 sq ft (about the area of one's hand or a quarter of the surface area of one's back), in any case may not be practical in ensuring an even spread of medicament.

11. Data derived for the product Evamist, also based on US Patent No. 6,916,486, further indicate a transdermal flupirtine product would not be efficacious. The product Evamist (containing estradiol: MW 272, log P 2.69) yields an average steady state plasma concentration for estradiol of 30.7 ng/L and 30.9 ng/L after 2 and 3 spays per day [12]. With a clearance of 30ml/min/kg [3], the estimated rate of delivery for estradiol transdermal absorption (plasma concentration X clearance) from a 20cm^2 area is 0.09 mg. If the surface area of application is increased to 40cm^2, one estimates an absorption rate of 0.18mg /day and to 800 cm^2, 3.6 mg.

12. The estimated maximum amount of flupirtine absorbed over a 24 hour period through human skin also suggests that transdermal flupirtine would not be efficacious. My previous calculations have used other drugs as a surrogate for flupirtine in estimating its absorption. Here, the direct transdermal penetration of flupirtine is examined using the most widely used skin penetration algorithm. This algorithm of Potts – Guy [13] overestimates the skin permeability when there are a number of hydrogen bond donors [14]; flupirtine has 10 hydrogen bonds: 5 freely rotatable, 6 acceptors and 4 donors. Flupirtine has a Potts-Guy estimated aqueous epidermal permeability of 1.8 X 10^{-7} cm sec^{-1} [15]. The amount of flupirtine absorbed through the skin over a 24 hr period from a saturated solution can be estimated as the aqueous epidermal permeability coefficient adjusted to per 24 hr X solubility in water (0.2mg/mL) [16]. This works out [17] to be 0.0031mg/24hr/cm^2 or assuming the largest possible area of application of 800cm^2, an amount absorbed over 24 hrs of 2.4 mg/24hr/cm^2, less than 1/100th of the lowest dose required for pharmacological activity. It is possible that increasing the absorption by super-saturation may have increased penetration further, but, in my experience [18], a typical enhancement one may expect in *in vivo* in humans for analgesics of

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12 http://www.evamist.com/pdf/Evamist_PI.pdf.

13 Potts RO; Guy RH. Predicting Skin Permeability, *Pharm Res* 9 (5) 663-669.

14 Fu *et al.* Limitation of Potts and Guy's model and a predictive algorithm for skin permeability including the effects of hydrogen-bond on diffusivity. *Pharmazie.* 2004 Apr;59(4):282-5.

15 log of flupirtine epidermal permeability = 0.71 X 1.986 -0.0061 X 304 – 6.3 = -6.744). Hence, its permeability coefficient = 10^-6.744 = 1.8 X 10-7 cm sec-1.

16 SciFinder Scholar calculations using Advanced Chemistry Development (ACD/Labs) Software V8.14.

17 24 hr amount absorbed for a unit area of 1 cm2 is 1.8 X 10-7 X 0.2*60(min)*60 (hr) X24= 0.0031mg/24hr/cm2.

18 Pellett *et al.* Supersaturated solutions evaluated with an in vitro stratum corneum tape stripping technique.

this type (e.g. the anti-inflammatory agent piroxicam) may be 4 fold. Hence, with an additional 4 fold increase due to the enhancer as disclosed in US Patent No. 6,916,486, one may project up to 1/5th of the lowest dose being attainable. This prediction is consistent with those made earlier by using similar type drugs as a surrogate.

13. Thus, as one who practices the art of advising on the design of topical products for therapeutic purposes, I conclude that it is not possible to apply the art defined by US Patent No. 6,916,486 to enable an adequate transdermal delivery of flupirtine to achieve the recommended daily doses of 300mg to 600mg for central analgesia in the treatment of peripheral neuropathy.

14. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful, false statements, and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: 10/3/09

MICHAEL STEPHEN ROBERTS

Date: 10/3/09 Witness

JEFFERY GRICE

International Journal of Pharmaceutics, Volume 151, Issue 1, 12 May 1997, Pages 91-98.